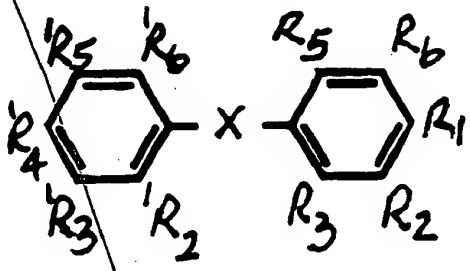
WHAT IS CLAIMED IS:

1. A method of modulating the activity of a thyroid hormone receptor (TR) which comprises administering to a mammal in need thereof a compound of the formula:



wherein said compound fits spatially and preferentially into a TR ligand binding domain (TR LBD) and comprises the following substituents:

(i) an R1-substituent comprising an anionic group that interacts with a side chain nitrogen atom of an arginine corresponding to a residue selected from the group consisting of Arg228, Arg262, and Arg266 of human TR-α, and Arg282, Arg316 and Arg320 of human TR-β, and wherein the anionic group is 1.7-4.0Å from the nitrogen atom;

(ii) an R2-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(iii) an R3-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a serine, alanine or isoleucine corresponding to a residue selected from the group consisting of Ser260, Ala263 and Ile299 of human TR-α, and Ser314, Ala317 and Ile352 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(iv) an R5-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a phenylalanine or isoleucine corresponding to a residue selected from the group consisiting of Phe218, Ile221 and Ile222 of human TR-α, and Phe272, Ile275 and Ile276 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(v) an R6-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(vi) an X-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a leucine corresponding to a residue selected from the group consisting of Leu276 and Leu292 of human TR-α, and Leu 330 and Leu346 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(vii) an R2'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(viii) an R3'-substituent comprising a hydrophobic group that interacts with a side chain atom of a phenylalamine, glycine or methionine corresponding to a residue selected from the group consisting of Phe215, Gly290, and Met388 of human TR-α, and Phe269, Gly344, Met442 of human TR-β, and wherein the hydrophobic group is 1.7-4.0Å from the side chain atom;

(ix) an R4'-substituent comprising an hydrogen bond donor or acceptor group that interacts with a side chain carbon or nitrogen atom of a histadine corresponding to residue His381 of human TR-α, and His435 of human TR-β, and wherein the hydrogen bond donor or acceptor group is 1.7-4.0Å from the side chain atom;

(x) an R5'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(xi) and R6'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

wherein said compound is other than a thyronine or thyronine-like compound disclosed in a reference cited in Appendix I, and wherein the activity of said TR is modulated.

2. The method according to claim 1,

wherein R_1 is

$-O-CH_2CO_2H$, $-NHCH_2CO_2H$,

$-CO_2H$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CO_2H$,

$-CH_2CH(NH_2)CO_2H$, $-CH_2CH[NHCOCH\phi_2]CO_2H$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]CO_2H$, $-CH_2CH[NH\text{-}FMOC]CO_2H$, $-CH_2CH[NH\text{-}tBOC]CO_2H$, or a carboxylate connected to the ring with a 0 to 3 carbon linker,

$-PO_3H_2$, $-CH_2PO_3H_2$, $-CH_2CH_2PO_3H_2$, $-CH_2CHNH_2PO_3H_2$,

$-CH_2CH[NHCOCH\phi_2]PO_3H_2$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]PO_3H_2$,

$-CH_2CH[NH\text{-}FMOC]PO_3H_2$, $-CH_2CH[NH\text{-}tBOC]PO_3H_2$, or a phosphate or phosphonate connected to the ring with a 0 to 3 carbon linker,

$-SO_3H$, $-CH_2SO_3H$, $-CH_2CH_2SO_3H$, $-CH_2CHNH_2SO_3H$, $-CH_2CH[NHCOCH\phi_2]SO_3H$,

$-CH_2CH[NHCO(CH_2)_{15}CH_3]SO_3H$, $-CH_2CH[NH\text{-}FMOC]SO_3H$, $-CH_2$

$CH[NH\text{-}tBOC]SO_3H$, or a sulfate or sulfite connected to the ring with a 0 to 3 carbon linker,

or acts as the functional equivalent of $CH_2CH(NH_2)CO_2H$ of T3 in the molecular recognition domain when bound to a TR, wherein said R_1 can be optionally substituted with an amine,

wherein R_2 is

H, halogen, CF_3, OH, NH_2, SH, CH_3, -Et,

or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein R_3 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et,

or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR,

wherein R_5 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR, and R_3 can be identical to R_5,

wherein R_6 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, -SH, $-CH_3$, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR, and R_2 can be identical to R_6,

wherein R_2' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein R_3' is any hydrophobic group, including

halogen, $-CF_3$, -SH, alkyl, aryl, 5- or 6-membered heterocyclie, cyano, or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR,

wherein R_4' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, NH_3, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, -SH, $-CH_3$, -Et, or akyl, aryl or 5- or 6-membered heterocyclic aromatic attached through urea or carbamate linkages to O or N or S at the R_4' position, or acts as the functional equivalent of OH in the molecular recognition domain when bound to a TR,

wherein R_5' is

-H, -OH, $-NH_2$, $-N(CH_3)_2$ -SH $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate, sulfate, branched or straight chain alkyl having 1 to 9 carbons, substituted or unsubstituted aryl, wherein said substituted aryl is substituted with halogen or 1 to 5

carbon alkyl and wherein said aryl is optionally connected to the ring by a $-CH_2-$, aromatic heterocycle having 5 to 6 atoms, wherein said heterocycle may be substituted with one or more groups selected from -OH, $-NH_2$, -SH, $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, heteroalkyl, arylalkyl, heteroaryl alkyl, polyaromatic, or polyheteroaromatic, wherein said R_5' may be substituted with polar or charged groups,

wherein R_6' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein X is

O, S, SO_2, NH, NR_7, CH_2, CHR_7, CR_7R_7, wherein R_7 is alkyl, aryl or 5- or 6-membered heterocyclic aromatic,

and wherein said TR LBD ligand has an apparent Kd for binding TR LBD of 1 μM or less.

3. The method of claim 2, wherein

R_1 is carboxylate, phosphonate, phosphate or sulfite and is connected to the ring with a 0 to 3 carbon linker,

R_2 is H,

R_3 is -I, -Br, or $-CH_3$,

R_5 is -I, -Br, or $-CH_3$,

R_6 is H,

R_2' is H,

R_3' is -I, -Br, $-CH_3$, -iPr, -phenyl, benzyl, or 5- or 6-membered ring heterocycles,

R_4' is -OH, $-NH_2$, and -SH,

R_5' is -H, -OH, $-NH_2$, $-N(CH_3)_2$ -SH $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate, sulfate, branched or straight chain alkyl having 1 to 9 carbons, substituted or unsubstituted aryl, wherein said substituted aryl is substituted with halogen or 1 to 5 carbon alkyl and wherein said aryl is optionally connected to the ring by a $-CH_2-$, aromatic heterocycle having 5 to 6 atoms, wherein said heterocycle may be substituted with one or more groups selected from -OH, $-NH_2$, -SH, $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, heteroalkyl, arylalkyl, heteroaryl alkyl, polyaromatic, or polyheteroaromatic, wherein said R_5' may be substituted with polar or charged groups, and

R_6' is H.

4. The method of claim 1, wherein said compound fits spatially and preferentially into TR LBD isoform α (TR-α).

5. The method of claim 4, wherein said compound comprises an anionic group that interacts with the side chain oxygen or carbon of a serine residue corresponding to Ser277 of human TR-α, and wherein the anionic group is 1.7-4.0Å from the side chain atom.

6. The method of claim 1, wherein said compound fits spatially and preferentially into TR LBD isoform β (TR-β).

7. The method of claim 6, wherein said compound comprises an anionic group that interacts with the side chain nitrogen of an arginine corresponding to Asn331 of human TR-β, and the anionic group is 1.7-4.0Å from the side chain atom.

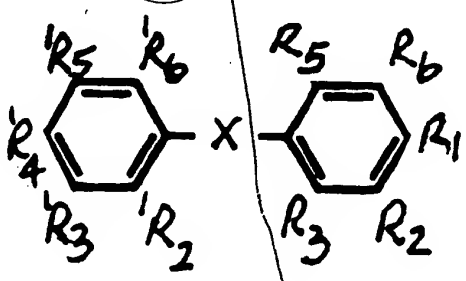
8. A method for identifying a compound capable of selectively modulating the activity of a thyroid hormone receptor (TR) isoform, said method comprising:

modeling test compounds that fit spacially and preferentially into a TR ligand binding domain (TR LBD) isoform of interest using an atomic structural model of a TR LBD isoform bound to a test compound,

screening said test compounds in a biological assay for TR isoform activity characterized by binding of a test compound to a TR LBD isoform, and

identifying a test compound that selectively modulates the activity of a TR isoform.

9. The method of claim 8, wherein said compound is of the formula:



which comprises the following substituents:

(i) an R1-substituent comprising an anionic group that interacts with a side chain nitrogen atom of an arginine corresponding to a residue selected from the group consisting of Arg228, Arg262, and Arg266 of human TR-α, and Arg282, Arg316 and Arg320 of human TR-β, and wherein the anionic group is 1.7-4.0Å from the nitrogen atom;

(ii) an R2-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(iii) an R3-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a serine, alanine or isoleucine corresponding to a residue selected from the group consisting of Ser260, Ala263 and Ile299 of human TR-α, and Ser314, Ala317 and Ile352 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(iv) an R5-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a phenylalanine or isoleucine corresponding to a residue selected from the group consisiting of Phe218, Ile221 and Ile222 of human TR-α, and Phe272, Ile275 and Ile276 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(v) an R6-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(vi) an X-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a leucine corresponding to a residue selected from the group consisting of Leu276 and Leu292 of human TR-α, and Leu 330 and Leu346 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(vii) an R2'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(viii) an R3'-substituent comprising a hydrophobic group that interacts with a side chain atom of a phenylalamine, glycine or methionine corresponding to a residue selected from the group consisting of Phe215, Gly290, and Met388 of human TR-α, and Phe269, Gly344, Met442 of human TR-β, and wherein the hydrophobic group is 1.7-4.0Å from the side chain atom;

(ix) an R4'-substituent comprising an hydrogen bond donor or acceptor group that interacts with a side chain carbon or nitrogen atom of a histadine corresponding to residue His381 of human TR-α, and His435 of human TR-β, and wherein the hydrogen bond donor or acceptor group is 1.7-4.0Å from the side chain atom;

(x) an R5'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD; and

(xi) and R6'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD.

10. The method according to claim 9,

wherein R_1 is

$-O-CH_2CO_2H$, $-NHCH_2CO_2H$,

$-CO_2H$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CO_2H$,

$-CH_2CH(NH_2)CO_2H$, $-CH_2CH[NHCOCH\phi_2]CO_2H$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]CO_2H$, $-CH_2CH[NH\text{-}FMOC]CO_2H$, $-CH_2CH[NH\text{-}tBOC]CO_2H$, or a carboxylate connected to the ring with a 0 to 3 carbon linker,

$-PO_3H_2$, $-CH_2PO_3H_2$, $-CH_2CH_2PO_3H_2$, $-CH_2CHNH_2PO_3H_2$,
$-CH_2CH[NHCOCH\phi_2]PO_3H_2$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]PO_3H_2$,
$-CH_2CH$[NH-FMOC]PO_3H_2, $-CH_2$ CH[NH-tBOC]PO_3H_2, or a phosphate or phosphonate connected to the ring with a 0 to 3 carbon linker,

$-SO_3H$, $-CH_2SO_3H$, $-CH_2CH_2SO_3H$, $-CH_2CHNH_2SO_3H$, $-CH_2CH[NHCOCH\phi_2]SO_3H$,
$-CH_2CH[NHCO(CH_2)_{15}CH_3]SO_3H$, $-CH_2CH$[NH-FMOC]SO_3H, $-CH_2$ CH[NH-tBOC]SO3H, or a sulfate or sulfite connected to the ring with a 0 to 3 carbon linker,

or acts as the functional equivalent of $CH_2CH(NH_2)CO_2H$ of T3 in the molecular recognition domain when bound to a TR, wherein said R_1 can be optionally substituted with an amine,

wherein R_2 is

H, halogen, CF_3, OH, NH_2, SH, CH_3, -Et,
or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein R_3 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et,
or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR,

wherein R_5 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR, and R_3 can be identical to R_5,

wherein R_6 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, -SH, $-CH_3$, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR, and R_2 can be identical to R_6,

wherein R_2' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein R_3' is any hydrophobic group, including

halogen, $-CF_3$, -SH, alkyl, aryl, 5- or 6-membered heterocyclie, cyano, or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR,

wherein R_4' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, NH_3, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, -SH, $-CH_3$, -Et, or akyl, aryl or 5- or 6-membered heterocyclic aromatic attached through urea or carbamate linkages to O or N or S at the R_4' position, or

acts as the functional equivalent of OH in the molecular recognition domain when bound to a TR,

wherein R_5' is

-H, -OH, $-NH_2$, $-N(CH_3)_2$ -SH $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate, sulfate, branched or straight chain alkyl having 1 to 9 carbons, substituted or unsubstituted aryl, wherein said substituted aryl is substituted with halogen or 1 to 5 carbon alkyl and wherein said aryl is optionally connected to the ring by a $-CH_2-$, aromatic heterocycle having 5 to 6 atoms, wherein said heterocycle may be substituted with one or more groups selected from -OH, $-NH_2$, -SH, $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, heteroalkyl, arylalkyl, heteroaryl alkyl, polyaromatic, or polyheteroaromatic, wherein said R_5' may be substituted with polar or charged groups,

wherein R_6' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein X is

O, S, SO_2, NH, NR_7, CH_2, CHR_7, CR_7R_7, wherein R_7 is alkyl, aryl or 5- or 6-membered heterocyclic aromatic,

and wherein said TR LBD ligand has an apparent Kd for binding TR LBD of 1 μM or less.

11. The method of claim 10, wherein

R_1 is carboxylate, phosphonate, phosphate or sulfite and is connected to the ring with a 0 to 3 carbon linker,

R_2 is H,

R_3 is -I, -Br, or $-CH_3$,

R_5 is -I, -Br, or $-CH_3$,

R_6 is H,

R_2' is H,

R_3' is -I, -Br, $-CH_3$, -iPr, -phenyl, benzyl, or 5- or 6-membered ring heterocycles,

R_4' is -OH, $-NH_2$, and -SH,

R_5' is -H, -OH, $-NH_2$, $-N(CH_3)_2$ -SH $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate, sulfate, branched or straight chain alkyl having 1 to 9 carbons, substituted or unsubstituted aryl, wherein said substituted aryl is substituted with halogen or 1 to 5 carbon alkyl and wherein said aryl is optionally connected to the ring by a $-CH_2-$, aromatic heterocycle having 5 to 6 atoms, wherein said heterocycle may be substituted with one or more groups selected from -OH, $-NH_2$, -SH, $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, heteroalkyl, arylalkyl, heteroaryl alkyl, polyaromatic, or polyheteroaromatic, wherein said R_5' may be substituted with polar or charged groups, and

R_6' is H.

12. The method of claim 8, wherein said compound fits spatially and preferentially into TR LBD isoform α (TR-α).

13. The method of claim 12, wherein said compound comprises an anionic group that interacts with the side chain oxygen or carbon of a serine residue corresponding to Ser277 of human TR-α, and wherein the anionic group is 1.7-4.0Å from the side chain atom.

14. The method of claim 8, wherein said compound fits spatially and preferentially into TR LBD isoform β (TR-β).

15. The method of claim 14, wherein said compound comprises an anionic group that interacts with the side chain nitrogen of an arginine corresponding to Asn331 of human TR-β, and the anionic group is 1.7-4.0Å from the side chain atom.

16. The method of claim 8, wherein said compound binds to a TR LBD isoform with greater affinity than thyronine or triiodothyronine.

17. A method for identifying a thyroid hormone receptor (TR) agonist or antagonist ligand, said method comprising the steps of:

providing the atomic coordinates of a TR ligand binding domain (TR LBD) to a computerized modeling system;

modeling ligands which fit spacially into the TR LBD; and

identifying in a biological assay for TR activity a ligand which increases or descreases the activity of said TR, whereby a TR agonist or antagonist is identified.

18. A peptide, peptidomimetic or synthetic molecule identified by the method of any one of claims 8 or 17, with the proviso that said molecule is other than a thyronine or thyronine-like compound disclosed in a reference cited in Appendix I.

19. A method of identifying a compound that selectively modulates the activity of a thyroid hormone receptor (TR) compared to other nuclear hormone receptors, said method comprising:

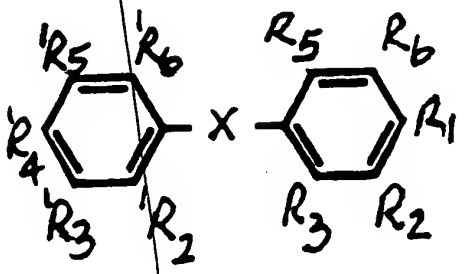
modeling compounds which fit spacially into a TR ligand binding domain (TR LBD) using an atomic structural model of a TR LBD,

selecting a compound comprising conformationally constrained structural features that interact with conformationally constrained residues of a TR LBD,

identifying in a biological assay for TR activity a compound that selectively binds to a TR LBD compared to other nuclear receptors, whereby a compound that selectively modulates a TR is identified.

20. The method of claim 19, wherein said conformationally constrained residues of a TR LBD correspond to residues Met259, Leu276, Leu292, His381, Gly290, Ile221, and Phe401 of human TR-α, and residues Met313, Leu330, Leu346, His435, Gly344, Ile275 and Phe455 of human TR-β.

21. The method of claim 19, wherein said compounds are of the formula:



which comprises the following substituents:

(i) an R1-substituent comprising an anionic group that interacts with a side chain nitrogen atom of an arginine corresponding to a residue selected from the group consisting of Arg228, Arg262, and Arg266 of human TR-α, and Arg282, Arg316 and Arg320 of human TR-β, and wherein the anionic group is 1.7-4.0Å from the nitrogen atom;

(ii) an R2-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(iii) an R3-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a serine, alanine or isoleucine corresponding to a residue selected from the group consisting of Ser260, Ala263 and Ile299 of human TR-α, and Ser314, Ala317 and Ile352 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(iv) an R5-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a phenylalanine or isoleucine corresponding to a residue selected from the group consisting of Phe218, Ile221 and Ile222 of human TR-α, and Phe272, Ile275

and Ile276 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(v) an R6-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(vi) an X-substituent comprising a hydrophobic or hydrophilic group that interacts with a side chain atom of a leucine corresponding to a residue selected from the group consisting of Leu276 and Leu292 of human TR-α, and Leu 330 and Leu346 of human TR-β, and wherein the hydrophobic or hydrophilic group is 1.7-4.0Å from the side chain atom;

(vii) an R2'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD;

(viii) an R3'-substituent comprising a hydrophobic group that interacts with a side chain atom of a phenylalanine, glycine or methionine corresponding to a residue selected from the group consisting of Phe215, Gly290, and Met388 of human TR-α, and Phe269, Gly344, Met442 of human TR-β, and wherein the hydrophobic group is 1.7-4.0Å from the side chain atom;

(ix) an R4'-substituent comprising an hydrogen bond donor or acceptor group that interacts with a side chain carbon or nitrogen atom of a histidine corresponding to residue His381 of human TR-α, and His435 of human TR-β, and wherein the hydrogen bond donor or acceptor group is 1.7-4.0Å from the side chain atom;

(x) an R5'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD; and

(xi) and R6'-substituent comprising a hydrophobic or hydrophilic group that fits spacially into the TR LBD.

22. The method of claim 19, wherein said compound comprises:

(i) a cyclic carbon atom that interacts with a carbon and oxygen atom of a methionine residue corresponding to Met259 of human TR-α, and Met313 of human TR-β, wherein the cyclic carbon is about 3.0 to 4.0Å from the carbon and oxygen atom of the methionine;

(ii) a cyclic carbon atom that interacts with a carbon atom of a leucine residue corresponding to Leu276 of human TR-α, and Leu330 of human TR-β, wherein the cyclic carbon is about 3.0 to 4.0Å from the carbon atom of the leucine;

(iii) a cyclic carbon atom that interacts with a carbon atom of a leucine residue corresponding to Leu292 of human TR-α, and Leu346 of human TR-β, wherein the cyclic carbon is about 3.0 to 4.0Å from the carbon atom of the leucine;

(iv) a R3-substituent comprising an atom that interacts with a carbon atom of an isoleucine residue corresponding to Ile221 of human TR-α, and Ile275 of human TR-β, wherein the R3-substituent atom is about 3.0 to 4.0Å from the carbon atom of the isoleucine;

(v) a R3'-substituent comprising an atom that interacts with an oxygen atom of a glycine residue corresponding to Gly290 of human TR-α, and Gly344 of human TR-β, wherein the R3'-substituent atom is about 3.0 to 4.0Å from the carbon atom of the glycine; and

(vi) a R4'-substituent comprising an atom selected from the group consisting of oxygen and carbon that interacts with (a) a carbon and nitrogen atom of a histidine residue corresponding to His381 of human TR-α, and His435 of human TR-β, wherein the R4'-substituent atom is about 2.0 to 4.0Å from the carbon atom of the histidine; and (b) a carbon atom of a phenylalanine residue corresponding to Phe401 of human TR-α, and human

Phe455 of TR-β, wherein said atom is about 3.0 to 4.0Å from the carbon atom of the phenylalanine.

23. The method according to claim 21,

wherein R_1 is

$-O-CH_2CO_2H$, $-NHCH_2CO_2H$,

$-CO_2H$, $-CH_2CO_2H$, $-CH_2CH_2CO_2H$, $-CH_2CH_2CH_2CO_2H$,

$-CH_2CH(NH_2)CO_2H$, $-CH_2CH[NHCOCH\phi_2]CO_2H$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]CO_2H$, $-CH_2CH[NH\text{-}FMOC]CO_2H$, $-CH_2CH[NH\text{-}tBOC]CO_2H$, or a carboxylate connected to the ring with a 0 to 3 carbon linker,

$-PO_3H_2$, $-CH_2PO_3H_2$, $-CH_2CH_2PO_3H_2$, $-CH_2CHNH_2PO_3H_2$,

$-CH_2CH[NHCOCH\phi_2]PO_3H_2$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]PO_3H_2$,

$-CH_2CH[NH\text{-}FMOC]PO_3H_2$, $-CH_2\ CH[NH\text{-}tBOC]PO_3H_2$, or a phosphate or phosphonate connected to the ring with a 0 to 3 carbon linker,

$-SO_3H$, $-CH_2SO_3H$, $-CH_2CH_2SO_3H$, $-CH_2CHNH_2SO_3H$, $-CH_2CH[NHCOCH\phi_2]SO_3H$, $-CH_2CH[NHCO(CH_2)_{15}CH_3]SO_3H$, $-CH_2CH[NH\text{-}FMOC]SO_3H$, $-CH_2\ CH[NH\text{-}tBOC]SO_3H$, or a sulfate or sulfite connected to the ring with a 0 to 3 carbon linker,

or acts as the functional equivalent of $CH_2CH(NH_2)CO_2H$ of T3 in the molecular recognition domain when bound to a TR, wherein said R_1 can be optionally substituted with an amine,

wherein R_2 is

H, halogen, CF_3, OH, NH_2, SH, CH_3, -Et,
or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein R_3 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et,
or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR,

wherein R_5 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR, and R_3 can be identical to R_5,

wherein R_6 is

-H, halogen, $-CF_3$, -OH, $-NH_2$, -SH, $-CH_3$, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR, and R_2 can be identical to R_6,

wherein R_2' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, $-N_3$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein R_3' is any hydrophobic group, including

halogen, $-CF_3$, -SH, alkyl, aryl, 5- or 6-membered heterocycle, cyano, or acts as the functional equivalent of I in the molecular recognition domain when bound to a TR,

wherein R_4' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, NH_3, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, -SH, $-CH_3$, -Et, or akyl, aryl or 5- or 6-membered heterocyclic aromatic attached through urea or carbamate linkages to O or N or S at the R_4' position, or acts as the functional equivalent of OH in the molecular recognition domain when bound to a TR,

wherein R_5' is

-H, -OH, $-NH_2$, $-N(CH_3)_2$ -SH $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate, sulfate, branched or straight chain alkyl having 1 to 9 carbons, substituted or unsubstituted aryl, wherein said substituted aryl is substituted with halogen or 1 to 5 carbon alkyl and wherein said aryl is optionally connected to the ring by a $-CH_2-$, aromatic heterocycle having 5 to 6 atoms, wherein said heterocycle may be substituted with one or more groups selected from -OH, $-NH_2$, -SH, $-NH_3$, $-N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, heteroalkyl, arylalkyl, heteroaryl

alkyl, polyaromatic, or polyheteroaromatic, wherein said R_5' may be substituted with polar or charged groups,

wherein R_6' is

-H, halogen, $-CF_3$, -OH, $-NH_2$, -SH, $-CH_3$, -Et, or acts as the functional equivalent of H in the molecular recognition domain when bound to a TR,

wherein X is

O, S, SO_2, NH, NR_7, CH_2, CHR_7, CR_7R_7, wherein R_7 is alkyl, aryl or 5- or 6-membered heterocyclic aromatic,

and wherein said TR LBD ligand has an apparent Kd for binding TR LBD of 1 μM or less.

24. The method of claim 23, wherein

R_1 is carboxylate, phosphonate, phosphate or sulfite and is connected to the ring with a 0 to 3 carbon linker,

R_2 is H,

R_3 is -I, -Br, or $-CH_3$,

R_5 is -I, -Br, or $-CH_3$,

R_6 is H,

R_2' is H,

R_3' is -I, -Br, $-CH_3$, -iPr, -phenyl, benzyl, or 5- or 6-membered ring heterocycles,

R_4' is -OH, -NH_2, and -SH,

R_5' is -H, -OH, -NH_2, -$N(CH_3)_2$ -SH -NH_3, -$N(CH_3)_3$, carboxylate, phosphonate, phosphate, sulfate, branched or straight chain alkyl having 1 to 9 carbons, substituted or unsubstituted aryl, wherein said substituted aryl is substituted with halogen or 1 to 5 carbon alkyl and wherein said aryl is optionally connected to the ring by a -CH_2-, aromatic heterocycle having 5 to 6 atoms, wherein said heterocycle may be substituted with one or more groups selected from -OH, -NH_2, -SH, -NH_3, -$N(CH_3)_3$, carboxylate, phosphonate, phosphate or sulfate, heteroalkyl, arylalkyl, heteroaryl alkyl, polyaromatic, or polyheteroaromatic, wherein said R_5' may be substituted with polar or charged groups, and

R_6' is H.

25. The method of claim 19, wherein said compound fits spatially and preferentially into TR LBD isoform α (TR-α).

26. The method of claim 25, wherein said compound comprises an anionic group that interacts with the side chain oxygen or carbon of a serine residue corresponding to Ser277 of human TR-α, and wherein the anionic group is 1.7-4.0Å from the side chain atom.

27. The method of claim 19, wherein said compound fits spatially and preferentially into TR LBD isoform β (TR-β).

28. The method of claim 27, wherein said compound comprises an anionic group that interacts with the side chain nitrogen of an arginine corresponding to Asn331 of human TR-β, and the anionic group is 1.7-4.0Å from the side chain atom.

29. The method of claim 19, wherein said compound binds to a TR LBD isoform with greater affinity than thyronine or triiodothyronine.

30. The method of claim 1, wherein said compound comprises a cyclic carbon atom that interacts with a carbon and oxygen atom of a methionine residue corresponding to Met259 of human TR-α, and Met313 of human TR-β, wherein the cyclic carbon is about 3.0 to 4.0Å from the carbon and oxygen atom of the methionine.

31. The method of claim 30, wherein said cyclic carbon is inner ring carbon C11.

32. The method of claim 1, wherein said compound comprises a cyclic carbon atom that interacts with a carbon atom of a leucine residue corresponding to Leu276 of human TR-α, and Leu330 of human TR-β, wherein the cyclic carbon is about 3.0 to 4.0Å from the carbon atom of the leucine.

33. The method of claim 32, wherein said cyclic carbon is selected from the group consisting of inner ring carbons C7 and C9.

34. The method of claim 1, wherein said compound comprises a cyclic carbon atom that interacts with a carbon atom of a leucine residue corresponding to Leu292 of human TR-α, and Leu346 of human TR-β, wherein the cyclic carbon is about 3.0 to 4.0Å from the carbon atom of the leucine.

35. The method of claim 34, wherein said cyclic carbon is selected from the group consisting of outer ring carbons C6 and C8.

36. The method of claim 1, wherein said R3-substituent comprises an atom that interacts with a carbon atom of an isoleucine residue corresponding to Ile221 of human TR-α, and Ile275 of human TR-β, wherein the R3-substituent atom is about 3.0 to 4.0Å from the carbon atom of the isoleucine.

37. The method of claim 1, wherein said R3'-substituent comprises an atom that interacts with an oxygen atom of a glycine residue corresponding to Gly290 of human TR-α, and Gly344 of human TR-β, wherein the R3'-substituent atom is about 3.0 to 4.0Å from the carbon atom of the glycine.

38. The method of claim 1, wherein said R4'-substituent comprises an atom selected from the group consisting of oxygen and carbon that interacts with a carbon and nitrogen atom of a histidine residue corresponding to His381 of human TR-α, and His435 of human TR-β, wherein the R4'-substituent atom is about 2.0 to 4.0Å from the carbon atom of the histidine.

39. The method of claim 1, wherein said R4'-substituent comprises an oxygen atom that interacts with a carbon atom of a phenylalanine residue corresponding to Phe401 of human TR-α, and human Phe455 of TR-β, wherein said atom is about 3.0 to 4.0Å from the carbon atom of the phenylalanine.

40. A method for identifying a thyroid hormone receptor (TR) agonist or antagonist ligand that selectively modulates the activity of a TR compared to other nuclear receptors, said method comprising the steps of:

providing the atomic coordinates of a TR ligand binding domain (TR LBD) to a computerized modeling system;

modeling ligands which fit spacially into the TR LBD and which interact with conformationally constrained residues of a TR LBD conserved among TR isoforms; and

identifying in a biological assay for TR activity a ligand which selectively binds to said TR and increases or decreases the activity of said TR, whereby a TR agonist or antagonist that selectively modulates the activity of a TR is identified.

41. A peptide, peptidomatic or synthetic molecule identified by the method of any one of claims 19 or 40, with the proviso that said molecule is other than a thyronine or thyronine-like compound disclosed in a reference cited in Appendix I.

42. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional

representation of a molecule or molecular complex for a thyroid hormone ligand binding pocket comprising structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Met259, Leu276, and Ile221, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

43. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex for a thyroid hormone ligand binding pocket comprising structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Leu292, His381, Gly290 and Phe401, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

44. The machine-readable storage medium according to any one of claims 42 or 43, wherein said binding pocket comprises structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Met259, Leu276, Leu292, His381, Gly290, Ile221 and Phe401.

45. The machine-readable storage medium according to claim 44, wherein said binding pocket comprises structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Arg228, Arg262 and Arg266.

46. The machine-readable storage medium according to claim 44, wherein said binding pocket comprises structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Ser260, Ala263 and Ile299.

47. The machine-readable storage medium according to claim 44, wherein said binding pocket comprises structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Phe218, Ile221 and Ile222.

48. The machine-readable storage medium according to claim 44, wherein said binding pocket comprises structure coordinates of TR-α amino acids corresponding to human TR-α amino acids Phe215, Gly290 and Met388.

49. The machine-readable storage medium according to claim 44, wherein said binding pocket comprises structure coordinates of a TR-α amino acid corresponding to human TR-α amino acid Ser277.

50. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex for a thyroid hormone ligand binding pocket comprising structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Met313, Leu330, and Ile275, or a homologue of said molecule or molecular

complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

51. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex for a thyroid hormone ligand binding pocket comprising structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Leu346, His435, Gly344, and Phe455, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

52. The machine-readable data storage medium according to any one of claims 50 or 51, wherein said binding pocket comprises structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Met313, Leu330, Leu346, His435, Gly344, Ile275 and Phe455.

53. The machine-readable data storage medium according to claim 52, wherein said binding pocket comprises structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Arg282, Arg316 and Arg320.

54. The machine-readable data storage medium according to claim 52, wherein said binding pocket comprises structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Ser314, Ala317 and Ile352.

55. The machine-readable data storage medium according to claim 52, wherein said binding pocket comprises structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Phe272, Ile275 and Ile276.

56. The machine-readable data storage medium according to claim 52, wherein said binding pocket further comprises structure coordinates of TR-β amino acids corresponding to human TR-β amino acids Phe269, Gly344 and Met442.

57. The machine-readable data storage medium according to claim 52, wherein said binding pocket comprises structure coordinates of a TR-β amino acid corresponding to human TR-β amino acid Asn331.

58. The machine-readable data storage medium according to claim 52, wherein said molecule or molecular complex is defined by the set of structure coordinates selected from the group consisting coordinates depicted in Appendix 3, 4, 5 and 6, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

59. The machine-readable data storage medium according to claim 52, wherein said molecule or molecular complex is defined by the set of structure coordinates selected from the group consisting coordinates depicted in Appendix 7 and 8, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

60. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates selected from the group consisting of coordinates depicted in Appendix 3, 4, 5, 6, 7 and 8; and said second set of data comprises an X-ray diffraction pattern of a molecule or molecular complex.

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